ACUTE TOXICITY SUMMARY

HYDROGEN FLUORIDE

(hydrofluoric acid (aqueous solution); hydrogen fluoride (gas))

CAS Registry Number: 7664-39-3

I. Acute Toxicity Summary (for a 1-hour exposure)

Inhalation reference exposure level	**240 μg/m³**
Critical effect(s)	irritation to the eyes, nose, and throat
Hazard Index target(s)	Respiratory System; Eyes

II. Physical and Chemical Properties (HSDB, 1994 except as noted)

Description	colorless liquid or gas
Molecular formula	HF
Molecular weight	20.01
Density	0.818 g/L @ 25°C (gas)
Boiling point	19.51°C
Melting point	-83.55°C
Vapor pressure	760 mm Hg @ 19.5°C
Flashpoint	not applicable
Explosive limits	not applicable
Solubility	soluble in water and alcohol
Odor threshold	0.042 ppm (geometric mean) (Amoore and Hautala, 1983)
Odor Description	strong, irritating odor
Metabolites	F^- (fluoride)
Conversion factor	1 ppm = 0.83 mg/m³ @ 25°C

III. Major Uses or Sources

Hydrofluoric acid (HF) is a colorless, fuming liquid with a sharp, penetrating odor (Fairhall, 1949). This acid is used in the glass etching, electronic, and chemical industries (Bertolini, 1992). These industries use HF in the manufacture of such things as metal cans, plastics, refrigerant chemicals, inorganic chemicals, soaps and detergents, high octane gasoline, and aircraft parts (Wohlslagel *et al.*, 1976; Wing *et al.*, 1991).

IV. Acute Toxicity to Humans

Hydrogen fluoride, an inorganic acid of fluorine, can cause both severe burns and systemic toxicity. Hydrogen fluoride produces dehydration and corrosion of tissues mediated by free hydrogen ions. In addition, the dissociated fluoride ion, F^-, also produces severe toxicity. The

fluoride ion complexes certain bivalent cations, primarily calcium and magnesium, to form insoluble salts. This interferes with the calcium metabolism in the underlying soft and bony tissues and results in cell destruction and severe pain. With severe HF burns, systemic toxicity may also result; hypocalcemia and hypomagnesemia are the most common manifestations (Bertolini, 1992).

Inhalation of HF causes coughing, choking, and chills lasting 1-2 hours after exposure; following an asymptomatic period of 1-2 days, pulmonary edema can occur with cough, chest tightness, rales, and cyanosis (Dreisbach and Robertson, 1987). Fatalities from HF inhalation may be due to pulmonary edema (ATSDR, 1993) and bronchial pneumonia (Dreisbach and Robertson, 1987). Acute aspiration of HF following facial splashes can cause bronchiolar ulceration, pulmonary hemorrhage and edema, and death (ATSDR, 1993).

Dermal exposures have resulted in death when as little as 2.5% of the body surface has come into contact with HF (Bertolini, 1992; Dreisbach and Robertson, 1987).

Largent (1961) describes the effects on 5 human volunteers of low-level HF exposures lasting 6 hours a day for 10-50 days. Each subject received a range of overlapping concentrations. The lowest concentration, 1.42 ppm (1.18 mg/m^3), produced no noticeable effects in one individual. Concentrations ranging from 2.59 to 4.74 ppm (2.15-3.93 mg/m^3) caused slight irritation of the face, nose and eyes, in addition to facial erythema apparently during the exposures. At 3.39 ppm (2.81 mg/m^3) "...an upper respiratory cold made the nasal passages hyper-irritable for a short time, and during this period burning in the nose produced by HF was the source of considerable discomfort" (Largent, 1961).

Wing *et al*. (1991) noted that hydrofluoric acid, in the form of a mist, can cause severe irritation of the eyes and respiratory tract, resulting in intense lacrimation, sore throat, cough, lower airway inflammation, and possible airway edema.

Lund *et al*. (1997) investigated eye and airway symptoms and lung function (forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC)) during and after a one hour exposure to hydrogen fluoride. Twenty healthy male volunteers were exposed in a chamber to constant HF concentrations that ranged from 0.2 to 5.2 mg/m^3. (Such concentrations occur among potroom workers in the primary aluminum industry, according to the authors.) The volunteers were asked to report itching or soreness of the eyes and upper airways and to grade these subjective responses on a scale from 1 to 5 with a standardized questionnaire. Lower airway symptoms of chest tightness and soreness, coughing, expectoration, and wheezing were similarly reported and graded by the volunteers. For the purposes of analysis the authors grouped the subjects into exposure groups of 0.2-0.6 mg/m^3 (low), 0.7-2.4 mg/m^3 (medium), and 2.5-5.2 mg/m^3 (high). Lower airway scores were not significantly different for any concentration range. The upper airway and total symptom score was significantly increased ($p<0.05$) at the end of exposure for the highest exposure range (2.5-5.2 mg/m^3, n=7) and for all exposures considered as a single group (0.2-5.2 mg/m^3, n=23). The total symptom score was also significantly increased at the end of exposure for the lowest concentration range (0.2-0.6 mg/m^3, n=9), although individual scores for eye irritation, upper respiratory irritation, and lower respiratory irritation were not significantly different comparing before and after exposure. Almost all the symptoms

had disappeared four hours after the end of exposure. Symptom scores from the upper airways were significantly correlated with the HF concentration ($r = 0.62$, $p = 0.002$), the change in plasma fluoride concentration (delta C) ($r = 0.51$, $p = 0.01$), and the maximum plasma fluoride concentration (Cmax) ($r = 0.42$, $p = 0.05$). A significant correlation was found between total symptom score for airways and the HF concentration ($p = 0.009$). No significant changes occurred in FEV_1 following exposure at any concentration. A statistically significant decrease in FVC (-0.02 L, 95% CI -0.5 to 0.06) was found in the group exposed at the lowest concentration range (0.2-0.6 mg/m³, n = 9). However, no dose-response relationship was evident and no lower airway symptoms were reported. The 0.7-2.4 mg/m³ range was considered to be a NOAEL and the range of 2.5-5.2 mg/m³ was deemed to be a LOAEL for upper airway irritation.

Predisposing Conditions for HF Toxicity

Medical: People with underlying cardiopulmonary disease may be more at risk from the irritating properties of HF at high concentrations on the lower airway.

Chemical: Unknown

V. Acute Toxicity to Laboratory Animals

In a study of the lethal effects of HF in mice, Higgins *et al*. (1972) determined a 5-minute LC_{50} of 6,427 ppm (5,334 mg/m³) while no lethality was observed after exposure to 2,430 ppm (2,017 mg/m³). The authors observed pulmonary edema in varying degrees of severity in most of the exposed mice. Pulmonary hemorrhage was a common finding in animals that died during, or shortly after, exposure to concentrations above the LC_{50} value. Higgins and colleagues also exposed rats to high concentrations of HF for 5-minute periods. Exposure of rats to 12,440 ppm (10,325 mg/m³) HF resulted in 10% mortality and exposure to 25,690 ppm (21,323 mg/m³) resulted in 100% mortality.

Wohlslagel and colleagues (1976) exposed rats and mice to HF for 60 minute durations. The 1-hour LC_{50} in mice, the most sensitive species, was 342 ppm (284 mg/m³), while no lethality was observed at 263 ppm (218 mg/m³). An exposure of 1,087 ppm (902 mg/m³) resulted in no lethality in rats, while 100% mortality was observed at 1,765 ppm (1,464 mg/m³). Wohlslagel *et al*. (1976) noted symptoms in both rats and mice which included eye and mucous membrane irritation, respiratory distress, corneal opacity, and erythema of exposed skin.

Rosenholtz *et al*. (1963) showed that rats and guinea pigs exhibited dose- and duration-dependent toxic effects from exposure to concentrations as low as 103 ppm (85 mg/m³) for 60 minutes. At this concentration, HF produced signs of irritation in rats, including pawing of the eyes and blinking. No histological damage to nasal or pulmonary epithelium, liver, or kidney was observed upon necropsy at this concentration. The signs resolved shortly after removal of the animals from the exposure chamber. Exposure to a concentration of 126 ppm (104 mg/m³) resulted in general discomfort, pawing at the nose, and tearing from the eyes. Most of the signs were mild and lasted for a few hours after exposure. Consequently, it was concluded that 103 ppm (85 mg/m³) represented a NOAEL for severe or disabling effects.

VI. Reproductive or Developmental Toxicity

There are no data available which describe reproductive effects in humans or animals, resulting from acute inhalation exposure to HF. Exposure of female rats to HF at 0.2 mg/m³ (0.24 ppm) was reported to be embryotoxic and teratogenic (Kenchenko and Saripova, 1974). The original study was not available for review.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 0.3 ppm (240 μg/m³)

Study	Lund *et al*. (1997)
Study population	20 healthy, male volunteers
Exposure method	inhalation of 0.2 to 5.2 mg/m³ HF (range) in an exposure chamber
Critical effects	upper respiratory tract membrane irritation
LOAEL	2.5-5.2 mg/m³
NOAEL	0.7-2.4 mg/m³
Exposure duration	1 hour
Extrapolated 1 hour concentration	2.4 mg/m³ (3 ppm)
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Reference Exposure Level	0.24 mg/m³ (240 μg/m³; 0.3 ppm)

Self-reported upper airway and eye irritation occurred after one hour of exposure to HF at 0.2-0.6 mg/m^3 with 4/9 subjects reporting low symptom scores. However, the scored symptoms were not statistically significantly different comparing before-exposure reported symptoms to after-exposure reported symptoms until concentrations exceeded 2.5 mg/m^3. The 0.7-2.4 mg/m³ range was considered to be a NOAEL and the range of 2.5-5.2 mg/m³ was deemed to be a LOAEL. While there were no changes in FEV_1, there was a slight decrease in FVC after exposure at the medium concentration range. However, OEHHA staff did not consider the changes in FVC to be significant adverse effects since there was no dose-response relationship and they were unaccompanied by changes in FEV_1 (see Section 3.2.1.1 in main text).

Level Protective Against Severe Adverse Effects

Following a 60-minute exposure to 103 ppm (85 mg/m³) HF, rats exhibited signs of mild irritation that resolved shortly after removal from exposure (Rosenholtz *et al*., 1963). Higher concentrations produced increasingly severe responses that persisted for hours after exposure. The 103 ppm (85 mg/m³) exposure was considered a NOAEL for severe effects. Application of

an uncertainty factor of 100 to account for interspecies and individual (human intraspecies) variation results in a level protective against severe adverse effects of 1.0 ppm (0.85 mg/m³).

The ERPG-2 for HF (20 ppm) is based on a report by Machle and Evans (1940) that workmen were exposed to HF in the range of 13-26 ppm (11-22 mg/m³) over a period of 9 years. The ERPG document also considered the animal lethality data from Machle *et al*. (1934) for development of the ERPG-2. The studies that form the basis for the ERPG-2 for HF are inappropriate. The study on workers by Machle and Evans (1940) did not examine irritation, kidney, liver, or lung function, but only skeletal fluorosis. In addition, the animal lethality data from Machle *et al*. (1934) is inappropriate for use as a basis for the ERPG-2, which is intended to protect nearly all individuals from serious or irreversible health effects. For these reasons, the ERPG-2 was rejected for use as a severe adverse effect level.

In comparison with the severe adverse effect level for HF, an alternative analysis yielded a level of 2 ppm that is protective against severe effects from a single 1-hour exposure to HF (Alexeeff *et al*., 1993). The results in this published paper provide support for the 1 ppm value calculated above to be protective against severe adverse effects.

Level Protective Against Life-threatening Effects

The ERPG-3 value for HF of 50 ppm (AIHA, 1992) is based on essentially two reports. The first, Machle *et al*. (1934), indicated that no deaths in rabbits or guinea pigs were observed following 30-minute exposures to 1,220 ppm (1,013 mg/m³) HF. The second report, an unpublished communication in the ERPG document, describes dangerous serum fluoride concentrations in humans exposed to 50 ppm (41.5 mg/m³) HF (Smith, 1988). However, the unpublished personal communication from Smith (1988) is not described in the ERPG documentation in sufficient detail for evaluation. There are some data indicating that mice and rats may be more sensitive to the acute lethal effects of HF than rabbits and guinea pigs (Wohlslagel *et al*., 1976). We did not choose to use the ERPG-3 as the level protective against life-threatening effects because of the inadequate explanation in the ERPG documentation.

In contrast to the qualitative estimate of the ERPG-3, the benchmark dose (BD) approach is presented below as a quantitative derivation. Wohlslagel *et al*. (1976) exposed mice to varying concentrations of HF for 60-minute intervals. The 1-hour LC_{50} value was determined to be 342 ppm (284 mg/m³) in mice. With these data, an exposure level was calculated by a BD approach using a log-normal probit analysis (Crump, 1983). The 95% LCL of the concentration expected to produce a response (in this case, lethality) rate of 5% was defined as the benchmark concentration (BC_{05}). The resulting BC_{05} from this analysis was 204 ppm (170 mg/m³). A UF of 3 was applied to account for animal to human (interspecies) extrapolation since use of the BC accounts for some degree of variation and a UF of 10 to account for human individual variation (intraspecies extrapolation).

level protective against life-threatening effects = BC/(UF)

The resulting value is 6.8 ppm (5.6 mg/m³). Based on comparison with the available literature on human studies, discussed above, this value appears to be an overly protective life-threatening effect level even for sensitive subpopulations. The appropriate level is probably between 7 and 50 ppm. Since neither value appears to be entirely appropriate, we chose a single point estimate within the range of these values, the geometric mean, or 19 ppm (15.5 mg/m³), as the level protective against life-threatening effects.

The maximum likelihood estimates (MLE) and 95% lower confidence limits (LCL) for the 1% and 5% mortality rates are compared below.

Comparison of 1% and 5% mortality rates for HF

Response rate	MLE (ppm)	95% LCL (ppm)
1%	216	166
5%	247	204

VIII. References

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